REMARKS

Reconsideration is requested.

Claims 1-13 have been canceled, without prejudice. Claims 14-56 have been added. Support for the amended claims may be found throughout the specification. No new matter has been added.

Specifically, the claimed method of treating nerve damage, such as damaged nerves of the peripheral nervous system, is described, for example, at page 5, lines 13-27 of the specification. Treatment by administration through use of a conduit placed around a damaged nerve is described at, for example, page 5, lines 13-23 of the specification. The recited MGF polypeptide of the claims is described, for example, in the paragraph spanning page 5, line 25 to page 6, line 3 of the specification and at page 9, lines 17 to 20 of the specification. The unglycosylated embodiment of the MGF polypeptide recited in the claims is described at page 9, lines 26-27 of the specification. The MGF polypeptides of the various embodiments of the claims are further described, for example, at page 10, line 15 to page 11, line 13; page 11, line 22 to page 12, line 11; page 13, lines 6-12; page 14, line 13 to page 15, line 1; page 17, line 16 to page 18, line 13. Methods for determining the recited sequence identity are described, for example, at page 18, line 15 to page 20, line 8 of the specification. No new matter has been added.

The specification has been amended to include the attached revised Abstract, as required by the Examiner in paragraph 5 of the Office Action dated November 20, 2002

(Paper No. 13). Moreover, the disclosure has been amended at page 19, line 11, to delete the browser-executable code, as required by the Examiner at paragraph 6 of Paper No. 13. Withdrawal of the objections to the disclosure is requested.

The acceptance of the drawings filed May 10, 2001, is acknowledged, with appreciation. See, box 10 on page 1 of Paper No. 13. The approval of the proposed drawing correction of December 14, 2001 is also acknowledged, with appreciation. See, box 11 on page 1 of Paper No. 13. Figures 9 and 10 were corrected with the Request of December 14, 2001 which included a revised formal and marked-up copies of Figures 9 and 10. Paper No. 13 indicates that if the requested drawing corrections are approved then corrected drawings are required in response to Paper No. 13. As noted above however, corrected drawings 9 and 10 have already been filed, and Paper No. 13 did not contain a Notice of Draftperson's Review (PTO 948) indicating what further may be required. The Examiner is specifically requested to advise the applicants what further may be required with regard to the drawings.

The Section 112, first paragraph, rejection of claims 1-6 and 9-11 is moot in view of the cancellation of the rejected claims. The pending claims are submitted to be supported by an enabling disclosure and the Examiner is requested to consider the following in this regard.

The claims provide methods of treating nerve damage by administering a MGF polypeptide. The applicants and others have previously detected MGF peptides in exercised or stretched skeletal muscles and overloaded cardiac muscle. See, page 2, lines

18-22 of the specification. These observations have led to a belief that MGF is involved in repair of damaged muscle. See, page 3, lines 6-10 of the specification and U.S. Patent No. 6,221,842 (Goldspink - attached hereto and listed on the attached PTO-1449 Form).

The applicants have now discovered that the MGF polypeptide of the claimed invention reduces motoneurone loss by as much as two times the reduction in loss found with L.IGF-1 (i.e., liver-type IGF-1) treatment. See, page 4, lines 14-24 of the specification. The applicants have discovered that the binding protein for MGF is located in the central nervous system (CNS) as well as skeletal and cardiac muscle, providing a basis for the demonstrated benefit of MGF in treating nerve damage, as compared with L.IGF-1. See, page 4, last paragraph of the specification. The applicants have demonstrated that by placing two ends of a severed rat sciatic nerve in juxtaposition in a conduit and filling with a gel comprising a vector containing MGF cDNA, repair of a 3mm gap in the nerve was achieved in as little as two weeks. See, page 5, lines 16-25 of the specification.

In Example 1 of the present application, the right facial nerve of experimental rats was avulsed (i.e., a simple tug to damage the nerve (see, page 34)). Regular (liver-type) IGF-I or MGF was then administered to the site of avulsion by expression of MGF from an MGF-encoding plasmid. With reference to page 33, lines 20-22 of the specification, such administration of MGF reduced motor neuronal loss following avulsion to 21%, i.e. by 79%. One of ordinary skill in the art is taught by the specification therefore how to make and use the claimed invention to produce a significant reduction in the damage

caused by the avulsion. MGF can thus be expected to have significant practical benefit in combating nerve damage.

Moreover, Example 2 (pages 35-36) of the specification demonstrates the utility of MGF in the treatment of severed nerves. Specifically, nerves were severed and conduits placed around the site of severance, said conduits comprising either a control plasmid, a plasmid capable of expressing regular liver-type IGF-I or a plasmid capable of expressing MGF. With reference to page 36, lines 14 to 17, expressing MGF led to vigorous regeneration throughout the width of the severed nerve, as demonstrated by staining in Figure 12. Figure 12 shows that little regeneration was seen in the control experiment, some in the IGF-I experiment and much more in the MGF experiment.

Accordingly, one of ordinary skill is taught by the present specification that MGF may be used to combat nerve damage, specifically avulsion and severance. The significance of Examples 1 and 2 however is not limited to these two specific sub-types of nerve damage. Rather, they show that MGF has beneficial properties regarding damaged nerves in general. Example 1 shows that MGF is capable of preventing loss of neurons in damage situations, whilst Example 2 shows that MGF is capable of stimulating re-growth of neurons. These properties can reasonably be expected to apply to nerve damage situations in general. An ordinarily skilled person reading the specification would understand that the claimed methods may be practiced without requiring an undue amount of experimentation.

As noted above, the presently claimed invention relates to a new use of MGF polypeptides for treatment of nerve damage.

The Examiner's reliance on Vejsada (Neuroscience, Vol. 84, No. 1, pp. 129-130 (1998)), Vejsada (European Journal of Neuroscience, Vol. 7, pp. 108-115 (1995)) and EP 308 386 to allegedly support the Examiner's enablement rejection is not understood and clarification is requested in the event the rejection is maintained.

The Examiner appears to rely on Vejsada (1998) as allegedly teaching that motoneurons are dependent on multiple growth factors. See, page 6 of Paper No. 13. Vejsada (1998) is not seen to have tested or discussed the activity of an MGF polypeptide of the presently claimed invention, but rather relates to brain-derived neurotropic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF).

As noted above, MGF polypeptides of the presently claimed invention include an insulin-like growth factor I isoform which has been found in exercised or stretched skeletal muscle. The fact that motoneurons may "respond to a variety of neurotropic factors" (see, page 6 of Paper No. 13) and "appear to be dependent on multiple growth and tropic molecules for normal development and/or maintenance" (see, page 6 of Paper No. 13) is, with due respect, submitted to be irrelevant to the issue of whether the applicants have taught those of ordinary skill in the art to treat damaged nerves with an MGF polypeptide of the claims. The applicants are not claiming the only method of treating damaged nerves, but rather a new use for a growth factor which was previously not recognized to have the novel activity claimed. The use of Vejsada's (1998) BDNF

or GDNF or Vejsada's (1995) neurotrophins (NGF, BDNF, NT-3 and NT-4) or cytokines (CNTF and LIF) to study these substances various effects on nerve rescue does not indicate that one of ordinary skill would believe an entire pathway or integrated effect of all possible means of treating or effecting nerve damage must be determined or elucidated before one of ordinary skill would reasonably expect to treat nerve damage with any one of these compounds if it was shown, as has been shown in the present application for MGF polypeptides, that loss of neurons may be prevented in damage situations and re-growth of neurons may be stimulated.

As for the Examiner's reliance on EP 0308 386 to allegedly teach an unpredictability of the effect of any peptide on any damaged nerves (see, page 7 of Paper No. 13), the applicants note that EP 0308 386 teaches the use of insulin-like growth factor (IGF-1) for "improving the regeneration of transected peripheral nerves in mammals and man." See, Abstract of EP 0308 386. As noted above and in the specification, a MGF polypeptide of the presently claimed invention was more than twice as effective at reducing motoneurone loss than L.IGF-1. See, page 4 of the present specification. Moreover, rather than teaching an unpredictability of effects of a variety of peptides on damaged nerves, as alleged by the Examiner, EP 0308386 appears to be focused on the effects of IGF-1 only, apparently based on an appreciation that Schwann cells in reactive nerves injured by sectioning or by crush exert positive influence on regeneration of peripheral nerve fibres and are a main source of IGF-1 after injury and are present extracellularly in the growth cone of regenerating nerves. See, page 4, lines

43-57 of EP 0308386. The present applicants improvement on the use of IGF-1 and comparison of MGF polypeptides with IGF-1 further supports the applicants belief that only a reasonable amount of experimentation would have been required to make and use the presently claimed invention.

The Examiner alleges that "even minor alterations to the protein structure have unpredictable effect on a proteins function". See, page 7 of Paper No. 13. The comment is apparently put forward as a general truth, as opposed to being supported by any specific evidence related to MGF polypeptides of the presently claimed invention. Whilst the Examiner's statement might be true in some cases, there will also be many minor changes that do not have such an effect. The present applicants are not claiming variant polypeptides in which changes detract from activity. The Examiner is urged to appreciate that the polypeptides of the presently claimed invention must have the ability to reduce motor neuron loss of 20% or greater in response to nerve avulsion. The specification teaches a method for testing such activity. Any MGF polypeptide which does not meet the functional criteria of the claims will not fall within the scope of the claimed invention. Structural requirements of the MGF polypeptides of the claims are clearly recited in the claims. Undue experimentation would not be required to make and use the claimed invention.

The Examiner appears to believe that an unreasonable degree of experimentation would be necessary to make and use MGF polypeptides of the claims. Identifying, making and using MGF polypeptides of the claims however would require no more than

a reasonable amount of experimentation. For example, an ordinarily skilled worked need only determine whether a particular MGF polypeptide is structurally defined by embodiments (b)-(e), for example, of claim 14, which is a simple paper exercise, involving use of the sequence information given in the specification in conjunction with routine experimental techniques to obtain the polypeptide, then test whether or not the MGF polypeptide has the properties required by the claims, for example using techniques along the lines of Example 1. Given that the claims recite regions 5/6 and 4/5/6, which distinguishes MGF from regular liver-type IGF-I, it is submitted that such experimentation is not undue.

Moreover, it is submitted that the amount of experimentation *per se* should not in any case be decisive; what is important is whether or not any such experimentation is routine or whether it requires the exercise of inventive skill. In the present case, any experimentation that may be required does not necessitate the ordinarily skilled person to make further inventions but merely to apply routine techniques known in the art or available in the specification and draw straightforward conclusions from the results.

In addition, the Examiner appears to suggest that the applicants must identify "all the applicable homologues" see, page 8 of Paper No. 13) or teach one or ordinary skill how to identify the same. Rather, the law requires the applicants to teach one of ordinary skill to make and use the claimed invention. A reasonable amount of experimentation may be required. The identification of MGF polypeptides within the claims would require no more than a reasonable amount of experimentation. The

applicants should not be required to "identify all the applicable homologues" to find the specification enables the claimed invention.

The Examiner's comments of paragraph 13 of Paper No. 13 appear to be moot in view of the amended claims.

Finally the Examiner's comment that the invention is "contrary to the teaching of the prior art" (see, sentence spanning pages 8-9 of Paper No. 13) is a reason the claimed invention is patentable over the art of record. The applicants comparison with and demonstrated improvement over the use of IGF-1 however provides further evidence that one of ordinary skill in the art would have a reasonable expectation that the claimed invention could be made and used without undue experimentation. See EP 038386 and above discussion of the same.

The Examiner's comment relating to alleged obstacles of target organ recovery (see, page 9 of Paper No. 13) appears to relate to the subject matter of now canceled claim 6. The concern is moot in light of the above amendments.

The Examiner's further concern regarding any effect of "MGF peptide" on nervous tissue is contrary to the experimental evidence of the present disclosure. Specifically, Examples 1 and 2 of the present specification demonstrate that a MGF polypeptide has an effect on nervous tissue, and Example 2 demonstrates nerve regeneration. The Examiner further alleges in page 9 of Paper No. 13 that a "large quantity of experimentation required to determine how to administer MGF peptides to achieve rejoining of severed peripheral nerves". Example 2 however of the specification

provides clear guidance, if any were needed, as to how this may be achieved, such as, by placing a MGF polypeptide within a conduit and placing the conduit around the site of injury. This is further discussed at pages 25 to 28 of the specification.

There would also be no obstacle to delivering the peptide in other ways, for example in a slow release gel such as the plutonic gel used by Morishita et al for buccal delivery of insulin (see attached: Morishita et al, Int. J. Pharm. 212, pp. 289-283, 2001). If the ordinarily skilled person elected not to use a conduit, he/she could instead, for example, suture the two ends of the nerve together using the perinerurium and apply such a gel, loaded with MGF polypeptide of the invention, to the sutures.

In view of the above and attached, the claims are submitted to be supported by an enabling disclosure.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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